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(54) Title: PREPARATIONS FOR THE APPLICATION OF ANTI–INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE LOWER RESPIRATORY TRACT

(57) Abstract

Use of an anti–inflammatory agent such as povidone iodine for the preparation of a pharmaceutical composition for the treatment of diseases of the lower respiratory tract which are susceptible to the administration of such agents.

Preparations for the application of anti-inflammatory, especially antiseptic agents and/or agents promoting the healing of wounds, to the lower respiratory tract

The invention concerns preparations for the application of agents with anti-inflammatory, especially antiseptic and/or wound healing promoting properties to the lower respiratory tract. The preparations are specifically applied to trachea, bronchi and alveoli in the lower respiratory tracts of humans and animals.

Furthermore, the invention concerns a method of preventing or treating infections by applying a pharmaceutical preparation.

A plurality of different antibiotic and antiseptic agents are known for the topical treatment of infectious maladies. A decisive disadvantage of antibiotic agents is that the infecting bacteria show primary resistances, and can acquire secondary resistances, against these agents. Further, antibiotics quite often lead to patient sensibilisation. The use of e.g. halogen-releasing antiseptics such as povidone iodine, also known as polyvidone iodine or PVP-iodine, i.e. the poly(1-vinyl-2-pyrrolidin-2-one)-iodine complex, can prevent resistances. Antiseptic agents are also much more rarely allergenic as compared to antibiotics.

At present, infectious diseases of the respiratory tract are treated with antibiotics. The application of antibiotic agents via the respiratory tract has been the subject of several reviews and articles with an emphasis on the lower respiratory tract. Ramsey et al., for example, describe the intermittent administration of inhaled tobramycin in patients with cystic fibrosis in "The New England Journal of Medicine", Volume 340, Number 1, 1999, p. 23-30.

been investigated for pulmonary delivery via liposomes include, e.g. anti-cancer agents, peptides, enzymes, anti-asthmatic and anti-allergic compounds and, as mentioned above, also antibiotics. The formulation of liposome aerosols or liposome powder aerosols using, for example a dry powder inhaler has also been described by H.

Schreier in "Formulation and in vitro performance of liposome powder aerosols" (S.T.P. Pharma Sciences 4, 1994, p.38-44).

Although a lot of attention has been paid to liposomes as drug carriers, as can be seen from the cited documents, there appears to be no prior art relating to liposomes and other particulates as carriers of anti-inflammatory, antiseptic and/or wound-healing promoting agents for applications in the body, especially in the lower respiratory tract, including the trachea, bronchi and alveoli.

Some of the prior art cited above is concerned with liposome preparations. It should be understood that alternative drug carriers of a similarly particulate character exist. These drug carriers can often -and also in the context of this invention- be used instead of liposomes and include microspheres (generally comprising lipophilic polymers), nanoparticles, "Large Porous Particles" and individually coated drug substance molecules, e.g. made by using pulsed laser deposition (PLD) techniques. These PLD methods can be used to apply coatings to drug powders and to modify surface properties and release rate to a variety of drug systems.

Where hereinafter reference is made to liposomes or particulate carriers, it is to be understood that this is to incorporate such alternative carriers, too.

In the context of this invention, antiseptic agents are understood to include those disinfecting agents which are pharmaceutically acceptable and suitable for the treatment of the lower respiratory tract to the extent that they can be formulated in accordance with the invention.

More specifically, antiseptic agents include inter alia oxygen- and halogen-releasing compounds; metal compounds, e.g. silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

Wound-healing agents comprise agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, and vitamine B-type compounds.

The invention is premised on the surprising fact that particulate carriers, especially liposomes, but also microspheres, nanoparticles and coated drug substance molecules, are highly suited as carriers for antiseptic agents, especially for povidone iodine, and for agents promoting the healing of wounds, for application to the lower respiratory tract.

The preparations according to this invention permit protracted release of the agent or agents, and provide an extended and topical activity at the desired locus of action by interaction with cell surfaces.

The invention is, another aspect, based on a further surprising and unexpected fact. It is well known in the art that the formation of new body tissues may cause problems. Thus, it is known that body tissue repair may be accompanied by the

compacted solid medicament reservoir. This medicament stock can then be abraded or micronized or treated in other ways to yield the powder in particle form. The resulting liposome preparation can be administered by inhalation of the preparation in the form of a powder aerosol, as, for example, described in "Acute Effects of Liposome Aerosol Inhalation on Pulmonary Function in Healthy Human Volunteers" (Thomas et al., Preliminary report, Volume 99, 1991, p. 1268-1270). The pressures for preparing the tightly compacted solid medicament stock are preferably in the range of from 50-500 MPa. Such medicament stock is described in WO 94/14490 and a device for administration is disclosed in WO 93/24165.

The nature or constitution of the liposomes is generally not critical. The liposome preparation as, for example, described in EP 0 639 373 can be administered by inhalation as an aerosol. The disclosure of EP 0 639 373 is incorporated by reference.

The preparations according to this invention apparently do not only contain the active agent, like povidone iodine, encapsulated in the particulate carrier, especially in liposomes. It seems that there is also some amount of agent which is not contained inside the carrier. The preparations according to the invention often show a marked initial effect which is observed in addition to the slower, protracted release of the active agent from the carrier. This effect is especially observed where the carrier comprises liposomes. Without wishing to be bound to any theoretical explanation, it is presently assumed that in addition to active agent encapsulated inside the liposomes, some active agent is present outside of the liposomes, and probably loosely bound to the outer surfaces of the liposomes. This could be due to association of active agent molecules with the liposomal membrane, or it could be due to active agent molecules forming a layer on the liposomal surface, which layer partly or even fully coats the liposome externally. The type and amount of this initial agent effect can e.g. be influenced by choice

Where alternative particulate carriers are used, they are generally prepared as known in the art. Thus, microspheres which are used to deliver a very wide range of therapeutic or cosmetic agents, are made as described for example in WO 95/15118.

Nanoparticles may in some cases be used, provided that they can be loaded with a sufficient amount of active agent and can be administered to the lower respiratory tract according to this invention. They can be prepared according to the methods known in the art, as e.g. described by Heyder (GSF München) in "Drugs delivered to the lung", Abstracts IV, Hilton Head Island Conference, May 1998.

Methods using a pulse laser deposition (PLD) apparatus and a polymeric target to apply coatings to drug powders in a short non-aqueous process are also suitable for the formation of particulate preparations according to this invention. These have e.g. been described by Talton et al., "Novel Coating Method for Improved Dry Delivery", Univ. of Florida UF 1887 (1998).

A further suitable delivery system employs Large Porous Particles as disclosed by David A. Edwards et al. in "Large Porous Particles for Pulmonary Drug Delivery" (Science, 20. June 1997, Vol. 276, p. 1868-1871). The average size of Large Porous Particles according to this invention can e.g. be in the range of between about 5 and 20 μm diameter for application to the alveoli.

Preferred anti-inflammatory agents comprise antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents, as single substances or in combination with each other.

Preferred antiseptic agents comprise the well-known pharmaceutical substances providing fast effect, a broad range of activity, low systemic toxicity and good

A presently highly preferred use of the inventive liposome preparations is in the treatment of infections of the lower respiratory tract, including trachea, bronchi and alveoli, especially when the liposome preparations contain povidone iodine. Also in this indication, the inventive antiseptic preparations, especially those containing PVP iodine, have the great advantage of not causing resistances and lead to much less allergic reactions, while permitting a very cost-efficient therapy with a broad spectrum of effect. A povidone iodine liposome preparation according to this invention is e.g. effective against viruses. Further, a liposome preparation of a microbicidal agent such as povidone iodine provides protracted release of the agent from liposomes delivering the agent to the pulmonary regions, for example to the alveolar regions of the lung. This leads to extended effect of the antimicrobial substance, and thus less frequent application, as compared with the customary antiseptic solution preparations.

The present invention is also useful in the treatment of infectious diseases or for alleviation of diseases such as HIV infections which are accompanied by opportunistic infections. Also patients having a suppressed immune system, for example, after organ transplants, can be treated according to the invention. In particular, acute and chronical bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria, tuberculosis can be treated with the povidone iodine preparation according to the invention.

Further highly preferred use is in tissue repair, especially in functional and cosmetic tissue remodelling.

Preparations according to this invention can take a variety of forms, which are suitable for administration via the lower respiratory tract, including pharmaceutically acceptable solid or liquid formulations, which are suitable for the generation of inhalable particles. Preparations according to this invention can be

The preparation will typically comprise at least 10 % wt of active agent such as PVP-iodine in the loaded liposomes (or alternative carrier particles), but may comprise up to 50 wt.-% or even more of active agent. Where the active agent is PVP-iodine, the amount of available iodine will generally be about 10 wt.-% (based on PVP-iodine).

More specific formulations are notable from the embodiment examples.

The features and advantages of this invention will become notable in more detail from the ensuing description of preferred embodiments. In these embodiments, which include a best mode, povidone iodine is exemplified as an antiseptic agent and liposomes are chosen as the carrier. This should, however, not be construed as a restriction of this invention to antiseptic agents or, among antiseptic agents, to povidone iodine, and/or to liposomes as the carrier, although such preparations are specifically preferred.

One preferred method for producing the invention's liposomes can generally be described as follows:

The lipid membrane-forming components, e.g. lecithin, are dissolved in a suitable solvent such as chloroform or a 2:1 mixture of methanol and chloroform and are filtered under sterile conditions. Then, a lipid film is produced on a sterile high surface substrate, such as glass beads, by controlled evaporation of the solvent. In some cases, it can be quite sufficient to form the film on the inner surface of the vessel used in evaporating the solvent, without using a specific substrate to increase the surface.

An aqueous system is prepared from electrolyte components and the (one or more) active agents to be incorporated in the liposome preparation. Such an aqueous

Embodiment Example I

In a 1000 ml glass flask, provided with glass beads for increased surface, 51.9 mg cholesterol and 213 mg hydrogenated soy bean lecithin were dissolved in a sufficient amount of a mixture of methanol and chloroform in a 2:1 ratio. The solvent was then evaporated under vacuum until a film was formed on the inner surface of the flask and on the glass beads.

2.4 g PVP iodine (containing about 10 % available iodine) were separately dissolved in 12 ml water.

Again in a separate vessel, 8.77 g sodium chloride and 1.78 g $Na_2HPO_4 \cdot 2H_2O$ were dissolved in 400 ml water. Further water was added up to a total volume of 980 ml, and then, approximately 12 ml 1N hydrochloric acid were added to adjust pH to 7.4. This solution was then topped up with water to exactly 1000 ml.

In a fourth vessel, 900 mg saccharose and 57 mg disodium succinate were dissolved in 12 ml water.

The PVP iodine solution was then added to the lipid film in the flask and the mixture was shaken until the film dissolved. The resulting liposome formulation was separated from the hydrated lipids in the flask. The product was centrifuged and the supernatant liquid was discarded. The saccharose solution was added ad 12 ml and the product was again centrifuged. Afterwards the supernatant liquid was again discarded. At this stage, a further washing step, using the saccharose solution or the sodium chloride buffer solution could be carried out.

After the last centrifugation step and discarding of the supernatant, 12 ml sodium chloride buffer solution was added, and the liposomes were homogenously

After the final centrifuging and decanting step, 40 ml sodium chloride buffer solution was again added to the precipitated liposomes. The homogenous dispersion was then distributed into vials, each vial containing about 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step. This produced approximately 200 mg freeze-dried solids per vial.

Like that of Embodiment Example I, the above-described method uses a hydrating step after film formation in the presence of organic solvents and aims at inclusion rates of 5 to 15 %. These methods generally produce rather large and often multi-lamellar liposomes.

The above-described methods can be modified by a high pressure filtering step through a suitable membrane such as a polycarbonate membrane after the raw liposomes have been formed or after any of the subsequent washing steps or directly by using high pressure homogenisation. This produces much smaller, unilamellar liposomes at increased amounts of encapsulated agent.

Instead of high pressure homogenisation, other prior art methods known to provide small uniform sized liposomes can be employed.

Embodiment Example III

A gelatine capsule, which is suitable for the generation of inhalable particles, was prepared from 20 g of povidone iodine liposomes containing leophilised (?????) material according to the above-mentioned general preparation method and 20 mg lactose by applying pressures of up to 500 MPa. From the obtained hard capsule a powder or powder aerosol was generated by abrading methods using a powder inhaler (Orbital-Inhaler by Brin Tech International Ltd.

staphilococci.

The results are shown in Table 1.

TABLE I

Contact Time (Minutes)	Bactericidal Concentration
1, 2, 3, 4	≥ 0.060 %
5, 30, 60	≥ 0.015 %
120	≥ 0.007 %

The results show that at short contact times (between 1 and 4 minutes) the bactericidal concentration is as low as 0.06 % and that at long contact times (120 minutes) the bactericidal concentration can be as low as 0.007 %.

Test II

The virucidal and chlamydicidal activity of liposomal PVP-iodine has been studied, in cell cultures, by Wutzler et al., 9th European Congress for Clinic Microbiology and Infection Diseases, Berlin, March 1999. In cell cultures, liposomal PVP-iodine is highly effective against herpes simplex virus type 1 and adenovirus tpye 8, while the long-term cytotoxicity experiments indicated that the liposomal form is better tolerated than aqueous PVP-iodine by the majority of cell lines tested. PVP-iodine in liposomal form is not genotoxic.

Test III

A 3% PVP-iodine hydrogel liposomal preparation was compared with a 3% PVP-iodine ointment, where the active agent was not in liposomal form. The agent

Claims

1. A process for the manufacture of a pharmaceutical preparation for the application of antiseptic agents and/or agents which promote the healing of wounds to the lower respiratory tract,
characterised in that the preparation contains at least one of said agents combined with a particulate carrier.

2. The process of claim 1,
characterised in that said particulate carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation or a laser-pulse polymer coated molecule preparation.

3. The process according to claim 1 or 2,
characterised in that at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

4. The process of any one of claims 1 to 3,
characterised in that the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines,

9. The process according to any one of the preceding claims, characterised in that the carrier particles, especially liposomes, have a substantially uniform size in the range between about 1 and about 50 µm, preferably in the range between about 1 and about 30 µm.

10. The process according to claim 9, characterised in that the carrier particles, especially liposomes, have a substantially uniform size in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm, especially between 2 and 5 µm, diameter for application to the alveoli.

11. The process according to any one of the preceding claims, characterised in that the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

12. The process according to claim 11, characterised in that the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

17. The process according to any one of the preceding claims, the preparation being in a suitable form for administration via the lower respiratory tract, which comprises:

a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and

b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

wherein the liposomes are of substantially uniform size between about 1 and about 50 µm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical formulation.

18. The process according to claim 17,

characterised in that the liposomes are of substantially uniform size, in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm diameter, preferably between about 2 and 5 µm diameter, for application to the alveoli.

19. The process according to any one of claims 1 to 18, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections

24. The method of claim 22 or 23, wherein said carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation, or a laser-pulse polymer coated molecule preparation.

25. The method of claim 22 or 23, wherein at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

26. The method of claim 23, wherein the anti-inflammatory agent is selected from antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents.

27. The method of claim 22 or 23, wherein the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

33. The method of claim 32, wherein the carrier particles, especially liposomes, have substantially uniform size in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm diameter, especially between 2 and 5 µm, for application to the alveoli.

34. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

35. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

36. The method of claim 22 or 23, wherein the preparation additionally comprises at least one anaesthetically active agent.

37. The method of claim 22 or 23, wherein the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

41. The method of claim 22 or 23, wherein the liposomes are of substantially uniform size, between about 20 and 30 μm diameter for application to the trachea, between about 10 and 20 μm diameter for application to the bronchi and between about 1 and 6 μm, preferably between about 2 and 5 μm diameter, for application to the alveoli.

42. The method of claim 22 or 23, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections or a suppressed immune system.

43. The method of claim 22 or 23, wherein the preparation is suited for the treatment of acute and chronic bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria and/or tuberculosis.